RESEARCH NEWS AND TRENDS FROM THE NATIONAL INSTITUTE ON DRUG ABUSE

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Computer-Based Interventions Promote Drug Abstinence

Interactive multimedia therapies may reduce costs and extend access to treatment.

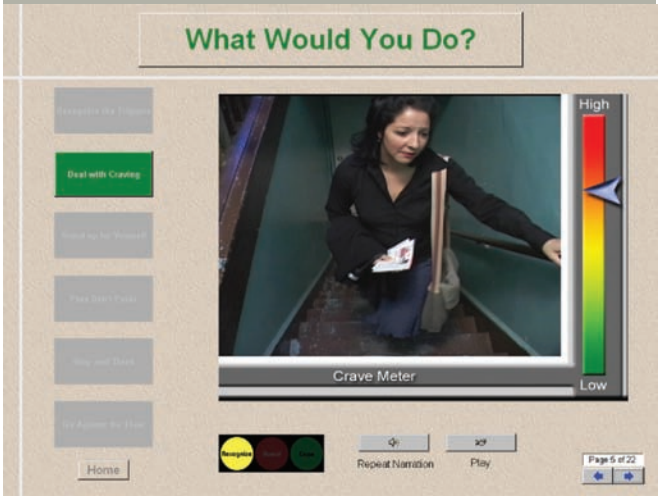
BY LORI WHITTEN,
NIDA Notes Staff Writer

Ever since Sigmund Freud first invited a patient to lie on a couch to talk things out, therapy has involved person-to-person communication. Recently, researchers have begun to harness the potential of computers to reinforce and expand upon the well-established benefits of therapy delivered by a counselor.

NIDA-funded researchers have developed and successfully tested interactive multimedia versions of three evidence-based therapies. Two of the programs enhanced outcomes when provided as adjuncts to standard treatment in community clinics. The third program reduced counselor input in community reinforcement therapy by 85 percent without loss of efficacy.

"Computers have revolutionized how we do business, and they may finally influence substance abuse treatment in a profound way," says Dr. Warren Bickel of the University of Arkansas for Medical Sciences, co-creator of one of the programs. Among the advantages he and others foresee are more strategic and effective use of counselors' time and skills and reduced treatment costs.

COPING WITH CRAVING The Computer-Based Training for Cognitive-Behavioral Therapy program uses interactive video to teach abstinence skills.



Computer-Based Training for Cognitive-Behavioral Therapy (CBT4CBT)
© Kathleen Carroll and Yale University

CHANGING ONE'S STORY

On the computer screen, Maria walks up the stairs to her apartment. She's confronted with a range of cues for drug use: a gift of cash, unpaid bills, and her boyfriend encouraging her to use. The movie then stops, and a narrator introduces the concept of coping with craving, which is then followed by several interactive exercises and games. Finally, the movie is shown again, but in this version Maria uses some of the strategies for coping with craving. She decides to take a walk to distract herself from craving and visits a friend who encourages her drug abstinence.

[*Continued on page 14*]

ALSO IN THIS ISSUE

By NORA D. VOLKOW, M.D., *NIDA Director*

Substance Abuse Among Troops, Veterans, and Their Families

Military experts are concerned that the wars in Iraq and Afghanistan may be precipitating a rise in problems related to substance use and abuse among the military personnel who have been deployed to those fronts. NIDA has joined forces with the Department of Defense, Department of Veterans Affairs, and other Federal agencies in a campaign to assess and find solutions to this threat to the health and well-being of our service men and women, veterans, and their families.

Demographic factors and the military's unique organizational structures, culture, and experiences contribute to service members' overall high prevalence of smoking and binge drinking and low prevalence of illicit substance abuse, when compared with civilian rates. The patterns of tobacco use illustrate the impact that war can have on substance use: Tobacco use is about 50 percent higher among the Nation's active duty military personnel and veterans than in the civilian population. Yet studies reported at a recent NIDA-cosponsored meeting indicate that smoking rates are an additional 50 percent higher among personnel who have served in war zones.

Combat exposure appears to be a primary mediator of the impact of war deployment on substance abuse rates. In one study, one in four veterans of Iraq and Afghanistan reported symptoms of a mental or cognitive disorder; one in six reported symptoms of post-traumatic stress disorder (PTSD). These disorders are strongly associated with substance abuse and dependence, as are other problems experienced by returning military personnel, including sleep disturbances, traumatic brain injury, and violence in relationships.

NIDA research has established effective principles for preventing and treating substance abuse and co-occurring problems and has proven the efficacy of a variety of interventions. This knowledge may provide a basis for reducing substance abuse and its consequences among the military. Modifications may be required, however. Ways will have to be found, for example, to counter some service members' reluctance to seek treatment, which may reflect a cultural emphasis on showing strength rather than needs, or perhaps worries about potential disciplinary consequences. We will need to learn how factors associated with deployment affect service members' risks for substance abuse and their recovery pathways. The high rates of co-occurring PTSD and substance abuse among those who have directly experienced combat have put a premium on research to develop stronger responses to these difficult problems.

NIDA and its coalition partners have issued a call for research on the epidemiology, causes, prevention, and treatment of substance use and abuse and co-occurring problems among service members, veterans, and their families (RFA-DA-10-001 and RFA-DA-10-002). In this and other efforts, NIDA is working with military and mental health specialists to help those who have served the Nation. ■

NIDA Notes

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Nicotine Boosts Mood, Brain Dopamine Levels

Just handling, lighting, and drawing on a cigarette can alleviate craving and anxiety in a person addicted to nicotine, NIDA researchers have found. Chronic smokers in a study led by Dr. Arthur Brody at the University of California, Los Angeles, reported relief from these withdrawal symptoms after smoking cigarettes that, unbeknownst to them, contained only trace amounts of nicotine. Another desired effect of smoking, a lift in mood, required fully nicotinized cigarettes, however.

Using positron emission tomography on the 62 study participants, the researchers correlated the degree of mood elevation with the size of the nicotine-triggered surge in levels of the neurotransmitter dopamine in the brain's main reward area, the ventral striatum. Standard cigarettes raised these levels an average of 8 percent, while denicotinized cigarettes increased them by only 1 percent.

Although the participants' reported decrease in cigarette craving did not correlate with smoking-induced changes in dopamine levels in the reward pathway, it may reflect dopamine activity in other parts of the brain or sensory aspects of cigarettes, says Dr. Brody.

> Neuropsychopharmacology 34(2):282-289, 2009.

Methamphetamine Turns Helper Cells Into Destroyers

Microglial cells support brain health by attacking infectious agents and clearing away damaged neurons, but too much microglial activity can initiate a biochemical cascade that assaults healthy neurons. Chronic methamphetamine abuse precipitates just such neurodegeneration, says Dr. Jean Lud Cadet of the NIDA Intramural Research Program.

Dr. Cadet and colleagues used positron emission tomography to document more than double the levels of activated microglia in all brain areas examined in 12 former methamphetamine abusers compared with 12 nonabusers. A lesser degree of excess glial activation was related to longer abstinence from the drug, suggesting that the abnormality resolves gradually. Individuals who had remained methamphetamine-free for 2 years exhibited activation levels similar to those measured in nonabusers.

> The Journal of Neuroscience 28(22):5756-5761, 2008.

Patch Delivers Buprenorphine for Heroin Detox

A patch that delivers buprenorphine across the skin for 7 days can alleviate newly abstinent heroin abusers' opioid withdrawal symptoms, report Dr. George Bigelow and colleagues at The Johns Hopkins University School of Medicine in Baltimore. The patch represents a new way to deliver buprenorphine during opioid detoxification; currently, the medication is most often given as a sublingual tablet. At Johns Hopkins, 12 heroin-dependent inpatients who were given patches experienced easing of cramps, flushing, nausea, and restlessness within 24 hours. Their symptoms continued to decline over the week and did not return after patch removal. Additional medications to ease withdrawal symptoms were available, but clinicians administered these rarely throughout the 10-day study. The patch is not yet clinically available, but if future studies prove its safety and effectiveness for general use, it may reduce problems with missed tablets and minimize concerns about diversion of the opioid agonist/antagonist.

> Psychopharmacology 198(2):149-158, 2008.

Methadone Therapy in Prison Benefits Men a Year Out

Providing methadone maintenance to men in prison can pay off in better retention in community treatment and reduced drug abuse following their release. In a recent clinical trial, men who began methadone therapy and counseling in prison and continued that treatment in the community had significantly lower rates of opioid-positive and cocaine-positive urine samples 12 months after being released,

compared with men who only received counseling and men who received counseling in prison and were scheduled to receive methadone maintenance upon release. As important as the lower rates of drug use, says researcher Dr. Timothy Kinlock of Friends Research Institute in Baltimore, was the methadone-maintenance group's longer retention in community-based treatment programs. The group assigned to begin methadone maintenance in prison stayed in community treatment an average of 166 days; the group scheduled to begin methadone maintenance upon release averaged 91 days. The men in the counseling-only group remained in community treatment for only 23 days.

> Journal of Substance Abuse Treatment 37(3):277-85, 2009.

Division of Epidemiology, Services and Prevention Research

DESPR Identifies Drug Abuse Trends and Seeks Solutions

BY NIDA NOTES STAFF

How many Americans abuse drugs and what are the costs to society? What strategies work best to prevent young people from becoming addicted to drugs? Are there ways to change the service delivery system that will improve success in preventing and treating drug abuse?

These questions fall within the purview of NIDA's Division of Epidemiology, Services and Prevention Research (DESPR). Dr. Wilson Compton, the division's director, says its broad mission is to track the Nation's drug use and provide empirically based information that researchers and service providers can use to prevent drug abuse and deliver treatment.

"DESPR is NIDA's primary interface with public health organizations, providing the latest information on the status of the national drug abuse situation," says Dr. Compton. The division supports the development and assessment of prevention interventions, the study of treatment services and potential improvements to their effectiveness, and epidemiological research to understand the status, patterns, trends, and determinants of drug-use behavior in the United States. DESPR comprises three branches: the Epidemiology Research Branch, the Services Research Branch, and the Prevention Research Branch.

"We look for patterns and take an analytic approach to addressing drug use and the associated health and behavior problems," Dr. Compton says.

THE EPIDEMIOLOGY RESEARCH BRANCH

Drug abuse patterns, trends, and pathways occupy this DESPR branch, which is currently headed by Acting Branch Chief Dr. Marsha Lopez. The branch considers the individual, developmental, social, and environmental factors associated with the course and outcomes of drug abuse.

The Epidemiology Research Branch, for example, oversees and manages the Monitoring the Future (MTF) survey, which is an important tool for epidemiologists, program planners, and policy officials who track U.S. drug abuse trends. This survey has been conducted annually since 1975 by the University of Michigan Institute for Social Research under a grant from NIDA. The MTF distributes a questionnaire to approximately 45,000 students in the 8th, 10th, and 12th grades nationwide.

From the MTF survey results, policymakers and researchers assess how well prevention interventions and policies are working. In August 2008, for example, when a group of college presidents recommended that the minimum drinking age be lowered to 18 because the increase to 21 "isn't working," MTF statistics showed otherwise, indicating that teen alcohol use had declined since the minimum alcohol-purchase age was raised in the 1980s.

Recently, the MTF survey drew attention to a new and disturbing trend: high school students abusing two prescription pain medications at increasing rates. In 2008, some 10 percent of high school seniors said they had abused Vicodin, and 5 percent reported abusing OxyContin. The findings prompted calls for renewed focus on the risks posed by abuse of prescription medications.

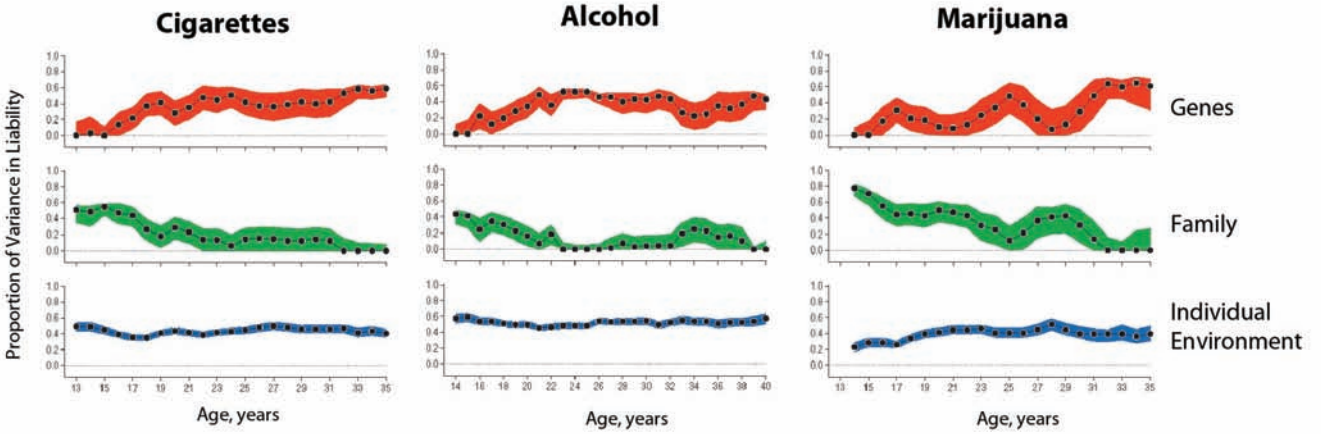
Each year the results of the MTF and other NIDA-funded epidemiologic studies provoke a fresh set of questions for DESPR. "The first question is: What new or ongoing problems are evident in the findings?" Dr. Compton says. "The next question is: What can we do about these problems?"

The Epidemiology Research Branch also oversees and manages NIDA-funded research on the genetic epidemiology of drug abuse. "We know that alcohol and drug abuse run in families," says DESPR Deputy Director Dr. Kevin Conway. "These studies aim to quantify the interplay of genetic and environmental factors in the tendency to abuse drugs." Recent studies performed under DESPR auspices suggest that besides influencing physiological responses to drugs, a person's genetic inheritance may increase his or her likelihood of choosing peers, relationships, and environments that make drug abuse more likely. Dr. Conway says, "This means that genetics and environment work together to increase or decrease risk."

Another challenge is to grasp how the still developing adolescent brain differs from that of the adult. NIDA research overseen by DESPR's Epidemiology Research Branch shows that adolescents are more likely than adults to experiment with drugs and that teens may be more addiction-prone than adults.

Dr. Conway says, "We plan to look at exposure to drugs in adolescence and the impact of that exposure on subsequent patterns of drug use and risk for addiction. Individual vulnerabilities that appear in early adolescence, for

SUBSTANCE USE INFLUENCED MORE BY FAMILY ENVIRONMENT EARLY IN LIFE AND GENETICS LATER ON With NIDA funding under the auspices of DESPR, researchers examined 1,796 pairs of male twins from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders. The vertical axes represent the contribution of genetic effects, family, or individual environment to observed variations in liability to drug use. The width of the colored lines at each point is one standard error, a measure of statistical uncertainity, above and below the point estimate.



Source: Kendler, K.S., et al. Genetic and environmental influences on alcohol, caffeine, cannabis, and nicotine use from early adolescence to middle adulthood. *Archives of General Psychiatry* 65 (6): 674-682, 2008. Copyright 2008 American Medical Association. All rights reserved.

example, might reveal prime targets for intervention."

THE SERVICES RESEARCH BRANCH

The goal of the Services Research Branch is to identify the most effective ways to organize, manage, finance, and deliver high-quality drug abuse prevention and treatment and related health services. The branch chief is Dr. Redonna Chandler.

This branch has overseen NIDA-funded studies demonstrating the value of drug and alcohol treatment services, particularly those integrated into comprehensive health care systems. For example, this research has shown that timely alcohol-counseling sessions for trauma patients can increase the number of participants entering alcohol treatment and dramatically reduce their alcohol consumption after they are released from the hospital. NIDA-funded work is now testing these approaches for drug abusers who receive care in trauma centers, emergency departments, and general medical settings.

THE PREVENTION RESEARCH BRANCH

Under the leadership of Drs. Elizabeth Robertson and Eve Reider, the Prevention Research Branch focuses on developing, testing, and applying interventions to deter drug use initiation or progression to abuse and dependence, as well as the transmission of HIV among drug-using populations.

The branch's current projects include several that address the well-documented link between aggressive behavior in a child's early school years and increased risk of problems later in life. "These are the kids who are alienated from classmates as soon as they start school," Dr. Compton says. "They fall in with other children who are at risk and adopt behaviors that make drug abuse more likely." The branch oversees research on programs designed to reduce aggressive behavior and facilitate children's effective functioning in school right from the start. The results indicate that interventions limited to high-risk children and interventions delivered to all children in a school regardless of their risk status can both be effective.

CHALLENGES ACROSS THE BRANCHES

DESPR also studies the interplay between drug use and other problems, such as mental or psychological disorders and HIV infection. These challenges involve all of the division's branches. "Human behavior is multifaceted and complex. Problem behaviors are not isolated factors that can be addressed in a vacuum," Dr. Compton says.

All three DESPR branches address the challenge of improving strategies for reducing HIV among drug abusers and their contacts. NIDA-funded research supervised by the Prevention Research Branch, for example, demonstrated that peer-educator outreach and the distribution of sterile injection equipment can lower the incidence of HIV infection. That 3-year study took place along the China–Vietnam border.

In a study overseen by the Epidemiology Research Branch, researchers at Yale University concluded that the public health and economic benefits of routine HIV testing in many medical settings would far outweigh the costs. Implementation of such testing may be more acceptable to the public than previously because stigmatization of infected individuals has eased.

A project under the auspices of the Services Research Branch showed that over more than a decade, outpatient drug treatment programs increasingly provided HIV testing and related services, but there is still a distance to go. "We know everyone entering drug treatment should be tested for HIV," Dr. Compton says, "but that is not happening yet." ■

Antibody Fragment Removes Methamphetamine From the Brain

Immune approach shows promise for treating overdose.

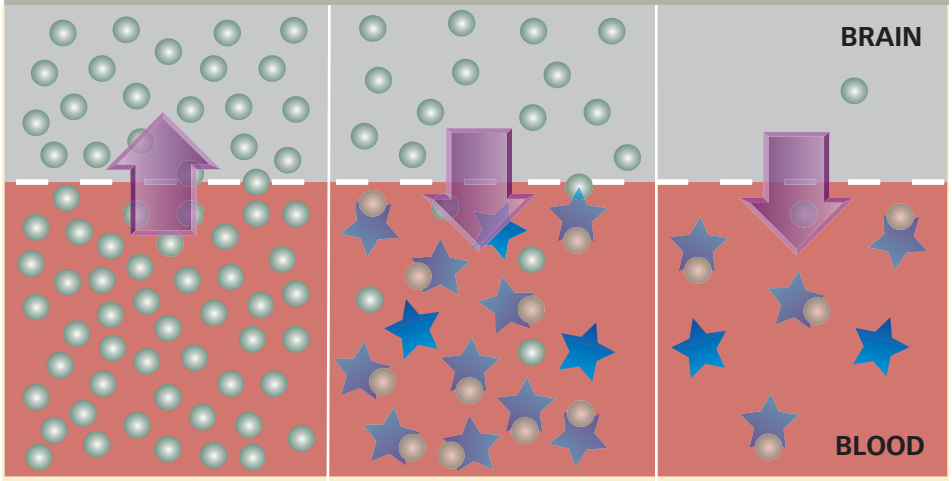
BY CARL SHERMAN,
NIDA Notes Contributing Writer

NIDA-sponsored researchers have produced an antibody fragment that rapidly removes the drug methamphetamine from the brain. This work in rats represents a major advance toward development of an effective therapy for methamphetamine overdose, a potentially life-threatening emergency that affects hundreds of Americans each year.

The fragment, called single-chain variable fragment 6H4 (scFv6H4), takes advantage of a physical property of methamphetamine and other small molecules: When their concentration in one compartment—for example, the blood—drops below their concentration in another compartment—for example, the brain—they will migrate from the higher to the lower concentration compartment until equilibrium is restored. When scFv6H4 is administered into the bloodstream, it lowers the concentration of free methamphetamine molecules by binding them into drug-antibody complexes. As the free drug concentration in the blood falls below that in the brain, where the antibody does not penetrate, molecules begin to flow out of the brain and into the blood. Once in the blood, these molecules, too, are captured by the antibody. Ultimately, the drug-antibody complexes are eliminated via the kidneys.

To create scFv6H4, researchers from the University of Arkansas for Medical Sciences started with a monoclonal antibody that they had previously derived from a natural mouse antibody that targets methamphetamine. From this monoclonal antibody, they produced a smaller molecule with similar affinity and specificity. Smaller forms of the antibody have some advantages over larger ones, an important one being that it is possible to put more of them into the bloodstream without the risk of causing adverse treatment effects. Because each antibody molecule attaches to just one methamphetamine molecule, physicians may have to administer high doses to bind the massive amounts of methamphetamine that are sometimes present in an overdose.

RAPID REVERSAL OF METHAMPHETAMINE OVERDOSE



Before Treatment
Molecules from a large dose of methamphetamine (green circles) circulate in the blood. Their natural tendency to distribute themselves evenly throughout accessible tissues causes many to move into the brain (arrow). As their concentration in brain tissue rises, symptoms of overdose occur.

During Treatment
Antibody fragments (stars) remove free methamphetamine molecules from the blood by binding them in drug-antibody complexes. As the concentration of free drug in the blood falls below that in the brain, the tendency to even distribution reverses the direction of molecular flow (arrow), so that drug now leaves the brain and reenters the blood.

End of Treatment
Methamphetamine molecules reentering the blood from the brain are in turn captured in drug-antibody complexes, keeping the process going. Ultimately, the kidneys eliminate the complexes.

DRAWING OUT THE POISON

To test scFv6H4, the researchers infused 10 rats with methamphetamine. After 3 days, when the rats had steady-state drug serum concentrations, the researchers injected half with scFv6H4 and the other half with an inactive solution. The results, they report, "were dramatic." Within the first minute after injection of the fragment, the concentration of serum methamphetamine—

including both free and fragment-bound—rose 65-fold, and it remained significantly elevated compared with that of the control animals for the next 4 hours. "The higher concentration in serum suggests lower concentration in the brain," University of Arkansas researcher Dr. Eric Peterson says.

The researchers also observed changes in the antibody fragment. Initially, 75 percent of the fragments were in the form of single molecules, or monomers. But these quickly joined together in twos, threes, and more to form compound molecules, called multimers. In just under 6 minutes following administration, half of the monomers had disappeared from serum—excreted via the kidneys, metabolized, or combined into more complex forms. The compound molecules, however, continued to draw methamphetamine from the tissues into the blood for several hours.

"The shift from monomers to multimers in vivo was the most surprising outcome," University of Arkansas researcher Dr. S. Michael Owens says. "Learning from that, we can redesign the fragment to produce complex forms that are optimally effective at binding methamphetamine."

DOUBLE PROMISE

"Now that we have antibodies with high affinity and specificity for methamphetamine, we are ready to go to the next generation of proteins, changing their biological properties to match therapeutic applications," Dr. Owens says. He points out that a product with a short half-life would be desirable in the treatment of overdose, when the goal is to quickly clear the drug from tissues. In contrast, a molecule that remains in the bloodstream long-term might serve as a basis for a vaccine to prevent relapse in individuals with methamphetamine dependence.

This research represents "incredibly significant progress," says Dr. Jamie Biswas, chief of NIDA's Medications Research Grants Branch in the Division of Pharmacotherapies and Medical Consequences of Drug Abuse. "There are, at present, no effective medications to treat methamphetamine-use disorders."

A good deal of work—toxicology testing, clinical trials, and the development of methods for large-scale production—remains to be done before methamphetamine immunotherapy becomes a reality. Dr. Biswas adds that a vaccine would probably work only for highly motivated patients. "In the face of strong craving, many users may attempt to overcome the effects of a monoclonal antibody or vaccine," she says.

"We will need to begin thinking about what treatments might make it easier for people to get off the drug with the help of a monoclonal antibody," she says. "This type of treatment may need to be augmented with other medications, such as antidepressants or antipsychotics, and/or behavioral therapy." ■

SOURCE

Peterson, E.C. et al. Development and preclinical testing of a high-affinity single-chain antibody against (+)-methamphetamine. *Journal of Pharmacology and Experimental Therapeutics* 325(1):124-133, 2008.

Smokers Who Quit May Have Genetic Advantage

Genes also seem to influence which smoking cessation technique works best for each person.

BY NIDA NOTES STAFF

Just about every smoker has trouble kicking the habit, but some have more trouble than others. Why? Part of the answer may lie in their genes, NIDA researchers say.

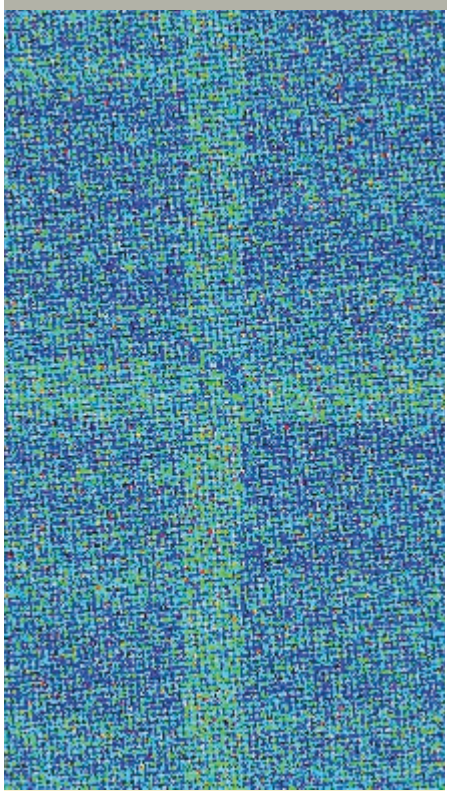
Dr. George Uhl and colleagues at NIDA's Intramural Research Program in Baltimore found more than 100 genes with DNA variants that distinguished smokers who quit successfully from others who tried to quit and failed. The team linked variants in other genes to the likelihood of success with specific smoking cessation therapies.

"It's as if there was a blueprint in your genetic code that spells out not only how easily you will be able to quit, but also might help us understand which therapy is right for you," says Dr. Uhl. "Matching individuals to the smoking cessation treatments that are most likely to benefit them could potentially have a huge public health impact."

GENES FOR SUCCESS

Dr. Uhl and colleagues conducted their study with DNA obtained from 550 European-American smokers between the ages of 18 and 65 who had received smoking cessation therapies in clinical trials at three universities. The smokers, who averaged about one pack of cigarettes per day, were given one of three therapies: nicotine patches, nicotine nasal sprays, or bupropion, an antidepressant that curbs nicotine cravings. Overall, 241 of the smokers achieved their goal of quitting and 309 did not.

DATA ON A CHIP The intensity of the signals on this chip, on a scale of white > red> orange > yellow > green > blue, indicates the presence of gene variants in a person's DNA. This fingernail-size chip simultaneously tests for more than 900,000 SNPs in a sample of human DNA.



The genes that distinguished successful from unsuccessful quitters differed with respect to single nucleotide polymorphisms (SNPs). SNPs are variants in DNA that are located at specific sites on a chromosome and occur in alternate forms in different individuals. Each gene the researchers identified as influencing quitting success incorporated at least two SNPs that 1) lay close to each other, 2) occurred more often in one form in successful quitters and more often in the alternate form in unsuccessful quitters, and 3) did so in at least two of the team's three studies. The team also found many genes that each contained a single SNP whose alternate forms were distributed unevenly between quitters and nonquitters; however, the researchers considered that these findings were likely to be chance occurrences.

The researchers identified 105 genes that met their criteria for designation as "quit-success" genes. They can now examine what role, if any, each of these genes plays in the biology of smoking cessation. Most are likely to individually contribute at most a little to quit success. A number of the genes highlighted are already known to contribute to a person's vulnerability to addiction to tobacco or other drugs and hence are likely candidates to also affect the ability to overcome addiction. Many of the genes produce proteins that figure prominently in important brain regions that addiction alters, such as the hippocampus, as well as in relevant biological processes, such as receptor and synapse formation and intercellular signaling.

Dr. Uhl and colleagues also identified 26 genes that may affect the chances of success with bupropion treatment, and 41 that may affect individuals' responses to the nicotine patch. The researchers' criterion for implicating these genes was the same as that used to identify overall quit-success genes: Each contains at least two SNPs having alternate forms that were distributed unequally between individuals who succeeded with the therapy and those who failed with it.

FIVE GENES LIKELY TO CONTAIN VARIANTS THAT CONTRIBUTE TO SUCCESS IN SMOKING CESSATION

Chromosome	Gene name	Role	Number of SNPs
3	RARB	Regulator of transcription	3
8	CSMD1	Cell adhesion molecule	10
10	PCDH15	Cell adhesion molecule	3
16	A2BP1	Regulator of mRNA splicing	3
21	DSCAM	Cell adhesion molecule	3

COMMUNITY CONFIRMATION

In a subsequent study, Dr. Uhl and colleagues confirmed the genetic influence on successful smoking cessation in a general community sample consisting of 480 men and women who volunteered for a National Institutes of Health research project. The volunteers—mostly European-American—reported their smoking histories, symptoms of nicotine dependence, and ability to successfully quit, though they did not report medications that they used as aids to quitting. A comparison of DNA from two subsets of these volunteers—120 current smokers and 100 successful quitters—indicated that variants in 67 genes distinguished the groups from each other. The results of genetic comparisons between smokers and successful quitters from the community volunteers overlapped with those from two of the three clinical-trial groups in Dr. Uhl's previous study. In particular, five genes were associated with successful quitting in both the community and clinical-trial samples. Many of these genes help neurons communicate and form connections.

Dr. Uhl's findings add to a growing body of research on the role that genes play in addiction and response to addiction treatment, says Dr. Ivan Montoya of NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse. NIDA is currently funding research to evaluate whether the success of treatments for smokers can be increased by selecting the treatment on the basis of the patient's genetic profile. Scientists are also looking for genes that affect individuals' responses to therapies for addiction to cocaine, methamphetamine, and marijuana, Dr. Montoya adds.

Dr. Uhl is optimistic that genetic tests to help smokers decide among quit-smoking medications will be available in 5 to 10 years. "Soon, your doctor or smoking cessation program will be able to provide you with a genetic score that will help you choose the strategy that gives you the best chance of quitting," he says. ■

SOURCES

Drgon, T. et al. Genome-wide association for nicotine dependence and smoking cessation success in NIH research volunteers. *Molecular Medicine* 15(1-2):21-27, 2009.

Uhl, G.R. et al. Molecular genetics of successful smoking cessation: Convergent genome-wide association study results. *Archives of General Psychiatry* 65(6):683-693, 2008.

Extended Cocaine Exposure Impairs Cognitive Function in Rats

Declines in a dopamine receptor parallel deficits in vigilance and mental flexibility.

BY LORI WHITTEN,
NIDA Notes Staff Writer

Do chronic cocaine abusers score lower than their peers on tests of concentration, short-term memory, and decisionmaking because the drug has impaired them? Or might they have done just as poorly before they ever took the drug?

NIDA-supported researchers Dr. Terry Robinson and colleagues at the University of Michigan recently presented strong evidence that cocaine causes cognitive deficits that can persist well into abstinence. In their study, rats that self-administered the stimulant performed worse than they had before taking the drug and worse than unexposed animals on a task requiring sustained attention and mental flexibility. The severity and persistence of the deficits correlated directly with the amount of drug exposure and inversely with levels of a neurotransmitter receptor that the drug suppresses.

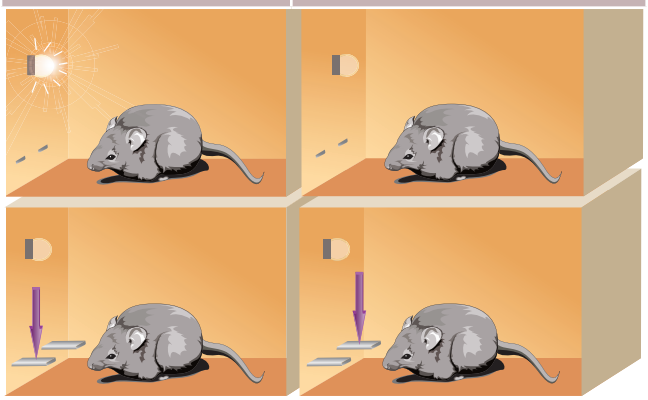
PERSISTENT PROBLEMS ON A DEMANDING TASK

The question of the etiology of cocaine abusers' cognitive deficits has important implications for prevention and treatment, but it is difficult to resolve through research with human subjects. To answer definitively, researchers would need to compare chronic abusers' current cognitive ability with baseline measures obtained before their first exposure to the drug. Yet such baseline measures are rarely, if ever, available. To obtain them, researchers would have to either accurately predict which unexposed young people are going to become chronic abusers or subject many young people to cognition tests.

The Michigan team avoided this obstacle by studying rats. They established baseline cognitive measures by training their animals up to a predetermined skill level on an experimental task. The task challenges the rat to choose correctly between two levers that are introduced simultaneously into its cage. Pushing on one lever is rewarded with a food pellet if a light flashed just prior to the appearance of the levers; pushing on the other lever is rewarded if the light did not flash (see illustration).

TESTS OF VIGILANCE AND MENTAL FLEXIBILITY

Signal Task	Non-Signal Task
After a half-second flash of light (top image), two levers emerge from the cage wall (bottom image). To receive a food pellet, the rat must press the lever on the left. This task requires sustained attention—the rat must remember and respond to a simple cue.	No light flashes, but two levers emerge from the cage wall. To receive a food pellet, the rat must press the lever on the right. This is considered harder than the signal task. The rat must apply a rule that is contingent on something not happening—i.e., the light not flashing—which requires cognitive flexibility.



Once each rat's lever responses reached roughly 70 percent overall accuracy, the researchers stopped the task and trained the animal to poke its nose into a hole to activate a mechanism that dispensed an infusion of cocaine. Six days every week for the next 3 weeks, some rats self-administered cocaine in this way for 1 hour per day and others for 6 hours per day. Three weeks in a rat's average lifespan is roughly proportional to a year or more in a human's. During this time, the rats in the 6-hour self-administration sessions progressively increased their intake to very high doses of the drug.

One day after a rat's final cocaine infusion, the researchers reintroduced the animal to the light-and-levers task. Animals that had self-administered the drug for 6 hours daily now pushed the wrong lever markedly more often than they had prior to taking the drug, and more often than a control group that had not been exposed to the drug. In contrast, animals that had self-administered cocaine for only 1 hour daily made roughly the same number of

Chronic Cocaine Self-Administration Increases Proportion of High-Sensitivity D_2 Receptors in Rats

Rats exposed to cocaine display a heightened sensitivity to stimuli that trigger dopamine release in the brain's striatum. When treated with a dopamine-promoting drug or test compound, for example, they increase their locomotor activity more than similarly treated cocaine-naïve animals do. These observations would be expected if cocaine increased the number of dopamine 2 (D_2) receptors, proteins that provide the primary points of access for the neurotransmitter to influence cellular activity in the striatum—a brain region that processes rewards and helps control movement. However, cocaine-exposed rats in laboratory studies have not consistently shown such increases. Moreover, imaging studies of people with histories of chronic cocaine abuse have found reduced, rather than augmented, striatal D_2 receptors.

Dr. Terry Robinson of the University of Michigan and colleagues, in collaboration with Dr. Philip Seeman of the University of Toronto, recently proposed a solution to this conundrum: On the basis of results they obtained in a recent study, the NIDA-funded researchers suggest that cocaine renders the rat striatum more sensitive to dopamine primarily by making some individual D_2 receptors more responsive, rather than by increasing their number.

Brain receptors, including the D_2 receptors, can change rapidly back and forth between two shapes. When the D_2 receptors are in the high-affinity shape (D_2^{High}), they bind more readily to dopamine and are more likely to become activated and affect brain function. "Our findings suggest that it's the functional state of the D_2 receptor that contributes to increased sensitivity and not the overall D_2 levels," says Dr. Seeman.

To assess cocaine's impact on D_2 functional states, rats in Dr. Robinson's lab were first trained to self-administer the drug and then allowed to do so for either 1 hour or 6 hours daily, 6 days per week. At the end of 4 weeks, Dr. Seeman and colleagues measured the rats' levels of D_2^{High} receptors. They found that both of these groups had more than double the proportion of D_2^{High} receptors in the dorsal striatum than a third group that had never received the drug. The D_2^{High} receptor elevation persisted at least 30 days after the last exposure to cocaine.

These results suggest a mechanism by which chronic cocaine may promote a return to drug seeking. A cocaine-induced increase in the proportion of dopamine-ready D_2 receptors could make the brain respond more strongly to the drug and its cues. Dr. Seeman's findings in rat brains indicate that the receptor's altered functional state may be a persistent neurobiological change underlying addiction.

The findings may also influence interpretation of current imaging studies in which cocaine abusers demonstrate lower D_2 receptor levels than nonabusers. "Our findings suggest that human imaging studies may not be capturing the complete picture of D_2 receptors," says Dr. Robinson. "The state of the receptor matters, so caution is required in interpreting human imaging results."

Currently, there is no way to differentiate the D_2 receptor's two forms in people. "Scientists are working on the very difficult task of finding a tracer for human imaging that selectively highlights the D_2 high-affinity state, but it will probably take years," says Dr. Seeman. "The implications of developing this tracer would be enormous, however. Appropriate radiotracers will clarify the role of the D_2 high-affinity state in cocaine addiction. Furthermore, the proportion of receptors in the high-affinity state may predict vulnerability to addiction." Along with addiction, D_2^{High} receptors may figure in the pathology of other psychiatric conditions, including schizophrenia.

"We hypothesize that the affinity state of the D_2 receptor fully accounts for the hypersensitivity to drug and drug-associated cues and explains why relapse is such a persistent problem," says Dr. Seeman. He and colleagues plan to examine the biochemical underpinnings of the shift from a low- to high-affinity state, and their findings may suggest future directions for therapy.

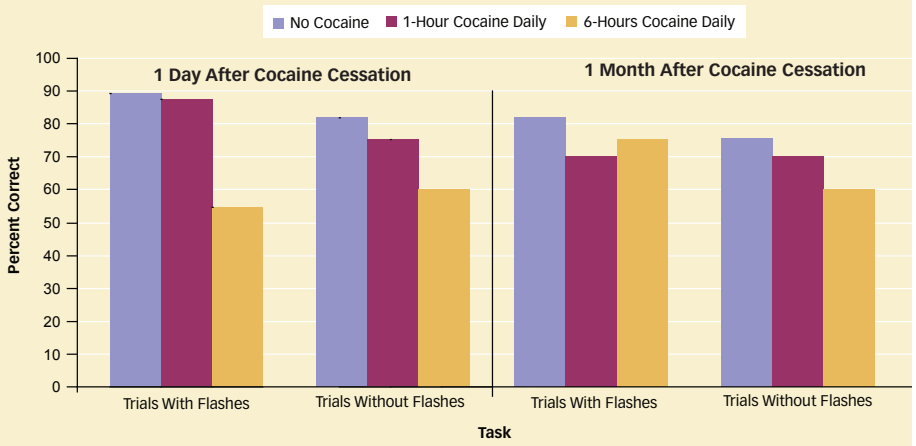
Source: Briand, L.A. et al. Cocaine self-administration produces a persistent increase in dopamine D_2^{High} receptors. *European Neuropsychopharmacology* 18(8):551-556, 2008.

errors as the control group. Retested again on post-cocaine days 14 through 21 or 28, the heavily exposed rats continued to exhibit impaired performance while those with less exposure scored as well as the control group.

The mistakes the rats made at the later retests primarily consisted of pushing the wrong lever when the light did not flash. This is reasonable, Dr. Robinson says, because choosing correctly in these instances calls on more complex cognitive abilities, particularly flexibility. "Making the correct choice after the light flashes requires attentiveness and the ability

to respond to a simple cue. When there is no light flash, the rat has to register its absence and recall an alternative rule for action. That's an ambiguous situation and therefore more cognitively demanding."

EXTENDED COCAINE ACCESS LEADS TO PERSISTENT ATTENTION DEFICITS One day after their final cocaine infusion, rats that had self-administered the drug in repeated, long bouts (6 hours daily for 3 weeks) were less accurate on a test of sustained attention than those that had short access (1 hour daily for 3 weeks) to the drug. One month after the last cocaine infusion, the performance of rats in all three groups was similar in responding to a half-second flash of light. Rats in the long-access group, however, were less accurate when presented with the more difficult problem of reacting to the absence of a light flash.



D_2 RECEPTOR LEVELS PARALLEL PERFORMANCE

Examination of brain tissue 4 days after their final cocaine infusion revealed fewer D_2 receptors in the prefrontal cortex (PFC) of those animals that had self-administered the drug in 6-hour daily sessions than of rats in the 1-hour-access and no-drug groups. In the medial area of the PFC, rats in the 6-hour-access group had D_2 receptor levels that were only about 85 percent those of the unexposed rats. Rats from the 6-hour-access group demonstrated continuing depression of D_2 receptor levels a month after cocaine self-administration stopped.

The D_2 receptor is one of several proteins that alter brain cell activity when stimulated by the neurotransmitter dopamine. Dopamine stimulation of D_2 receptors in the PFC contributes to a variety of cognitive functions, including attention, that come into play during decisionmaking. Although the results of Dr. Robinson's study suggest that cocaine may diminish cognitive functions by disrupting D_2 receptors, the larger picture of the drug's influence on these receptors is more complicated (see box, page 11).

THE IMPORTANCE OF PROTOCOL

Dr. Robinson's team is the first to investigate cocaine's effects on cognition using a self-administration protocol that results in drug intake comparable to that of human abusers. This feature of their study, says Dr. Robinson, is the reason they were able to demonstrate persistent cocaine-induced cognitive deficits. Other studies in which researchers gave animals more limited access to the drug have also observed deficits, but only transient ones. Also, previous research has shown that only extended access to cocaine is likely to induce behavioral and neural changes that are linked with addiction and relapse.

"Our findings suggest that extended cocaine self-administration changes the brain in a way that impairs the ability to be attentive."

—Dr. Terry Robinson

"Our findings suggest that extended cocaine self-administration changes the brain in a way that impairs the ability to be attentive—a capacity that is important in making decisions in real life," says Dr. Robinson. "The trials with flashes tested relatively simple cognitive processes, while the trials without flashes drew on more complex processes. Moreover, the mixing of trials with flashes and trials without flashes also taps into cognitive flexibility: The rats learned two different responses and had to execute the right one in each trial."

"This animal study used a well-designed, rich task to demonstrate persistent cocaine-induced deficits in important cognitive functions—sustained attention and cognitive flexibility—and link them to a neurobiological change," says Dr. Susan Volman of NIDA's Division of Basic Neuroscience and Behavioral Research. "Similar impairments in people would likely influence judgment and the ability to respond flexibly to the environment." ■

SOURCE

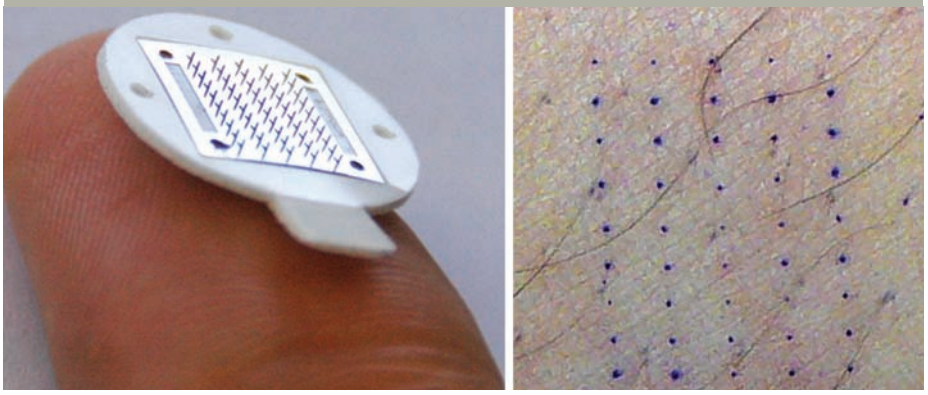
Briand, L.A. et al. Persistent alterations in cognitive function and prefrontal dopamine D_2 receptors following extended, but not limited, access to self-administered cocaine. *Neuropsychopharmacology* 33(12):2969-2980, 2008.

Naltrexone via Skin Patch Proves Effectiveness of New Technology

Microneedles will enable transdermal delivery of more medications.

BY LORI WHITTEN,
NIDA Notes Staff Writer

TINY NEEDLES PREPARE SKIN FOR PATCH MEDICATION A microneedle array (left) is a small rectangle of 50 tiny needles, each 620 microns in length and thinner than a human hair. Tiny, painless epidermal punctures created by pressing the needles against the skin act as conduits for medication to flow evenly from a skin patch into dermal capillaries and the bloodstream.



Dime-size arrays of tiny needles enabled volunteers to receive naltrexone via skin patch in a recent proof-of-concept clinical trial. If further work bears out the trial's success, the opiate antagonist and many other medications that are currently given orally or by injection may someday be administered by skin patch. In addition to avoiding painful needles and hard-to-swallow or stomach-irritating pills, transdermal delivery's advantages include well-controlled doses and steady medication blood levels over extended periods.

Pharmaceutical researcher Dr. Audra Stinchcomb and clinical pharmacist Dr. Daniel Wermeling of the University of Kentucky and engineer Dr. Mark Prausnitz of the Georgia Institute of Technology developed the new technology. Pressed painlessly into the skin, their microneedles puncture the relatively impermeable outer layer of epidermis to create a grid of pores through which medication can readily and evenly pass from a skin patch to the skin's capillaries and into the bloodstream. The team opted to test the technology with naltrexone, a medication used to treat alcohol and opiate abuse, because current oral and injected methods of administering the opiate antagonist have drawbacks.

In the trial, a research assistant applied four arrays of microneedles to the upper-arm skin of six healthy volunteers for a few seconds. The participants reported that the arrays did not hurt and felt smooth against their skin. After removing the microneedles, the assistant fastened a naltrexone transdermal patch over the same area with small bandages.

Because transdermal medication does not pass through the digestive system before entering the bloodstream, it reaches target tissues without being exposed to degradation by liver enzymes. As a result:

- Therapeutic blood levels were achieved with 12.6 mg of naltrexone per day, which is only about a quarter of a typical oral dosage.
- The volunteers' blood naltrexone concentrations began to rise within minutes of the patch application, stabilized at an average of about 2.5 ng/mL within hours, and remained relatively constant for 2 days; after 72 hours, they had fallen by about half but were still in the range considered therapeutic. With oral medication, blood naltrexone levels take longer to rise and may fluctuate widely between doses, sometimes falling to levels that are therapeutically ineffective and sometimes spiking to levels that cause adverse effects.
- Naltrexone was converted to its primary metabolite, naltrexol, at a much slower rate than that measured with oral administration. Because high naltrexol levels have been correlated with adverse effects and patient drop-out, keeping the levels low may enable more patients to tolerate naltrexone therapy.

The microneedle array was well-tolerated. Four patients developed redness and irritation at the site of the patch, which the researchers found to be due to the medication rather than the needles and which resolved during 2 weeks of

[*Continued on page 16*]

COMPUTER-BASED INTERVENTIONS

[*Continued from page 1*]

Maria demonstrates the challenges and choices of recovery in Computer-Based Training for Cognitive-Behavioral Therapy (CBT4CBT), an interactive multimedia program developed and copyrighted by Dr. Kathleen Carroll and colleagues at Yale University School of Medicine. CBT4CBT closely follows the content and session structure of manualized evidence-based cognitive-behavioral therapy. Its six lesson modules train patients to recognize and avoid situations that put them at high risk for abusing drugs, to refuse offers of drugs and alcohol, to cope with craving, and to make decisions that assist abstinence. Each module addresses one core concept. Each contains a movie with voiceover commentary, presents skill-building information, uses quizzes and games to reinforce and assess learning, and ends with a practice assignment.

In an 8-week trial, 35 patients in a community substance abuse clinic who spent time with CBT4CBT before twice-weekly sessions of the clinic's standard counseling submitted more drug-free urine samples than 38 patients who received only counseling (66 percent versus 47 percent). The CBT4CBT patients tended to have longer urine-confirmed continuous drug-free periods—averaging 22 days, compared with 15 days among the counseling-only patients. In the half-year following treatment, the CBT4CBT patients gradually reduced the number of days per month that they abused drugs, and their longest periods of continuous abstinence averaged 102 days. In contrast, the counseling-only patients' monthly days of drug abuse gradually climbed, and their longest abstinences averaged 73 days.

The trial's success in a community clinic population of abusers of diverse substances—participants' primary drugs of abuse included cocaine, alcohol, opioids, and marijuana—suggests that the CBT4CBT program may prove a valuable adjunct for many treatment programs. Patients liked the program, giving it a mean satisfaction score of 4.3 on a scale of 5.

One factor making CBT4CBT effective, Dr. Carroll suggests, may be that the program prepares patients to focus on their most acute concerns and problems when they meet with their clinicians. Moreover, she points out, CBT4CBT always delivers CBT with a high degree of fidelity, whereas clinicians sometimes stray from the model, with potential loss of impact.

ON-SCREEN ROLE PLAYING IN "WHAT IF" SCENARIOS

A voice says: "Watch the video and try and pick out the refusal skills." On the screen, three people on the front porch of a house talk to a young woman. One man says, "Hi, Kate, come here. We were just about to get high. You in?" Kate responds: "No, I'm not using anymore. It causes me too many problems." As Kate refuses, she looks unsure, sounds hesitant, and stares at the ground. The voice explains how Kate could make her refusal stronger, and the scene is repeated with Kate acting more assured, sounding firm, and looking directly at the man on the porch. Each subsequent version of the scene adds more elements of effective drug refusal.

Substance abuse patients view Kate's encounter and other educational vignettes in an interactive multimedia version of Community Reinforcement Approach with Vouchers therapy (CRA+). The program—developed by Dr. Bickel, Dr. Lisa Marsch of National Development and Research Institutes and St. Luke's–Roosevelt Hospital Center, and technology specialists—uses video simulations, voiceovers, quizzes, and games to help patients achieve a strategic goal of CRA+: improved social relationships that deliver enough satisfaction to offset the craving for drug highs. Program modules address family relationships and job-related problems and promote participation in healthy recreational activities and social networks. Patients learn and rehearse drug refusal and abstinence promotion skills. Among the more than 70 topics offered are self-management, prevention of HIV infection, and financial management.

The CRA+ program facilitates the therapeutic use of urine sampling by directly interfacing with the clinic's urinalysis equipment. Negative urine samples cue the machine to print out vouchers for monetary amounts that vary according to a predetermined schedule that is calculated to reinforce patients' motivation to stay abstinent. When a urine sample tests positive, the program identifies the type of drug and, through interactive exercises, assesses the circumstances of abuse

DEVELOPING DRUG REFUSAL SKILLS Community Reinforcement Approaches with Vouchers therapy helps patients improve their social relationships, which encourages drug abstinence.

Community Reinforcement Approach with Vouchers therapy (CRA+) © HealthSim LLC

and develops a customized plan for the patient to avoid future abuse. It also sends an e-mail report on recent drug abuse to the patient's counselor. As the patient completes work on the modules, the program provides feedback to the patient and reports to the counselor.

In a 23-week trial at a university research center, opiate abusers maintained on buprenorphine did equally well with either computerized or counselor-delivered CRA+. The trial participants attended three half-hour treatment sessions per week, but one group always met with a counselor while the other spent five out of six sessions at a computer working independently with CRA+. The latter group met with a counselor every sixth session to review progress and select new modules. At the end of the trial, the groups' average longest durations of continuous abstinence were essentially the same, slightly less than 8 weeks. Their outcomes surpassed those of a third comparison group that received counseling modeled on the standard regimen in methadone clinics. Those patients, whose counselors focused on participants' current problems, treatment progress, and program rules in one 37-minute session per week, attained an average longest duration of continuous abstinence of 5 weeks.

"People addicted to heroin often need to develop basic life skills, and they require help with a broad set of severe problems," says Dr. Bickel. "Our computerized therapy program incorporates evidence-based approaches from addiction treatment and educational research to offer patients a way to learn these skills."

THE POWER OF THE WHITE COAT

The doctor on the computer screen speaks warmly and respectfully. "I'm concerned that your current drug use may be putting your overall health at risk. My hope is that the information I'm about to share will support you in making decisions about drug use that are best for you." She asks about willingness to quit, and if the patient's responses show ambivalence, she says: "I know it's not easy to make that decision. Many people say they have mixed feelings. I would encourage you to continue thinking about this. It can be helpful to ask yourself some questions and write down answers: What do I like about drug use? What don't I like about drug use? If I continue, what effect will it have on my life? What will be the effect if I quit?"

DECIDING TO QUIT DRUGS The Video Doctor gently encourages HIV-positive patients to stop abusing illicit drugs.

Video Doctor © Regents of the University of California, San Francisco

The Video Doctor dispenses information about health risks and motivational messages to HIV-positive patients as part of a computerized program called Positive Choice. Rather than focusing on potential transmission of the virus, she—in reality an actress—emphasizes the potential consequences of drug abuse, unprotected sex, and other behaviors for the general health and quality of life of people living with HIV. The program aims to overcome factors that often impede HIV risk assessment and counseling, such as physicians' and patients' discomfort talking about sexual practices and drug abuse and patients' fear of stigma.

Clients log on to Positive Choice in a private area of a clinic about 1 hour prior to meeting with their physicians. If a client reports a risky behavior, such as drug abuse or unprotected sex, the program introduces the Video Doctor. She conducts a brief intervention that is based on the principles of motivational interviewing. The intervention is tailored by selecting the most appropriate from among a large set of files and film clips—featuring followup questions from the Video Doctor, facts about risks, suggestions for risk reduction strategies, and motivational messages.

A Video Doctor session takes most clients about 24 minutes to complete. At the end, the client receives a printed worksheet that reviews the main points of the conversation and suggests next steps. The client's physician receives a "cueing sheet" to guide discussion during the in-person visit that follows. This printout summarizes the client's risky behaviors, suggests counseling messages to reduce risk, and lists treatment centers for referral.

The researchers tested the Video Doctor at five HIV clinics in the San Francisco area. Of the 471 clients who participated in the study, roughly half were introduced to the Video Doctor, and the others received their clinic's usual treatment. All had reported at least one risky behavior on the Positive Choice initial assessment. The participants were ethnically diverse: 29 percent white, 50 percent black, 13 percent Hispanic, and 9 percent of other or mixed heritage; 21 percent were women, 29 percent were heterosexual men, and 50 percent were men who have sex with men.

Three months after the start of the study, roughly 33 percent of the Video Doctor users reported no current illicit drug use. The rate of illicit drug abuse also dropped among patients who did not use the Video Doctor, but only by 18 percent. Clients in the Video Doctor group reused the program during the 3-month followup. Three months after this booster session, the percentage of those reporting no illicit drug use rose to 44 percent. The rate among the comparison group, in contrast, remained essentially unchanged at the 6-month followup from what it had been at the 3-month mark.

"The Video Doctor program is a way around the time crunch in busy clinics, and our results show that the intervention works and fits easily into the clinic routine," says Dr. Barbara Gerbert, University of California, San Francisco, who helped develop the program. These strong results prompted the Centers for Disease Control and Prevention (CDC) to include the Video Doctor in its compendium of evidence-based interventions to prevent HIV infection.

"Clinics can use the Video Doctor in their CDC-funded activities. This is a special accomplishment that few NIDA grantees achieve," says Dr. Richard Jenkins of NIDA's Division of Epidemiology, Services and Prevention Research.

IMPROVING ACCESS TO INTERVENTIONS

"In a treatment system with limited funds, we should use the counselors for care that only they can provide—resolving family or employment problems, for example—and for patients who do not respond to computerized interventions," Dr. Bickel says. He notes that the patients who received the computerized CRA+ in his study and those who instead received therapist-delivered CRA+ reported forming equally strong bonds with their clinicians.

Along with cost savings, computerized adjunct interventions promise to increase access to treatment. Counselors who delegate some of their routine clinical functions to computers will be able to schedule more patients. Ultimately, patients who do not wish to go to a clinic or have difficulty doing so—for example, those who fear stigma or are poor, disabled, or located too far away—may be able to obtain some therapy wherever they can access a computer.

"Feedback from addiction treatment programs in the community has driven the development of computer-based adjuncts," says NIDA's Dr. Cecelia McNamara Spitznas of the Division of Clinical Neuroscience and Behavioral Research. "These treatment programs are under pressure to cut costs and maintain quality services, and computerized interventions—along with Web-based training for clinicians in proven treatments—may help them provide good care with limited resources.

"The resolve to quit is ephemeral for many drug abusers," says Dr. Spitznas. "But if help-on-demand is available through technology, we can seize on that motivation to engage patients in a longer term treatment process." ■

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NALTREXONE VIA SKIN PATCH

[*Continued from page 13*]

antihistamine treatment.

The trial demonstration represents a first step toward medical use of microneedles. The researchers next plan to look for a commercial partner and further refine the device.

"Many medications—those that are water-soluble, made of small molecules, or not easily absorbed orally—would be good candidates for microneedle-array delivery," says Dr. Wermeling. "The microneedle technology also opens up noninjection delivery for other therapeutic agents—including proteins, DNA, and vaccines—an advantage that is particularly exciting."

"Microneedle technology is part of a larger effort by NIDA-funded researchers to develop safer ways to deliver medications," says Dr. Moo Park of the Institute's Division of Pharmacotherapies and Medical Consequences of Drug Abuse. He notes that the new technology might increase patients' willingness to receive some important medical interventions, including vaccines. "Many patients avoid or are anxious about vaccine injections, and microneedle delivery of these important therapies has a promising future," he says. "The research is in the early stages but is an interesting area to watch." ■

SOURCE

Wermeling, D.P. et al. Microneedles permit transdermal delivery of a skin-impermeant medication to humans. *Proceedings of the National Academy of Sciences* 105(6):2058-2063, 2008.

R. Christopher Pierce Receives the Waletzky Memorial Award

Dr. R. Christopher Pierce, associate professor of neuroscience in psychiatry at the University of Pennsylvania School of Medicine, is the recipient of the 2008 Jacob P. Waletzky Memorial Award for Innovative Research in Drug Addiction and Alcoholism. He delivered the keynote lecture at NIDA's Frontiers in Addiction Research miniconference at the Society for Neuroscience Annual Meeting in Washington, D.C., on November 14, 2008.

Dr. Pierce's research has explored the long-lasting cellular changes that occur in response to chronic cocaine abuse. Dr. Pierce and colleagues traced a molecular chain of events in which cocaine stimulation of dopamine receptors in the nucleus accumbens enhances the expression of specialized glutamate receptors whose proliferation promotes a return to drug-seeking by animals previously weaned from it. Identification of this pathway may facilitate the development of relapse-prevention medications.

Dr. Pierce is also studying deep brain stimulation as a possible treatment for severe cocaine abuse. Stimulating areas of the brain affected by chronic cocaine abuse may alleviate craving and reduce relapse. Deep brain stimulation is widely used to treat Parkinson's disease, and scientists are testing this surgical procedure as a therapy for severe depression.

The Waletzky award carries an honorarium of $25,000 and is presented each year to a scientist who attained a doctoral degree in the past 15 years; it is intended to encourage innovative research into the neurobiology of drug addiction. The Waletzky family established the award in 2003 in memory of Jacob P. Waletzky, who died at age 29 of cocaine-induced cardiac arrhythmia.

Annual Event Teaches Students Brain Science

Some 750 students from Washington, D.C., and surrounding areas learned about brain anatomy and function, as well as dysfunction, from a series of hands-on activities during Brain Awareness Week, March 16-20. NIDA sponsored two of the activities held at the National Museum of Health and Medicine in Washington, D.C.

BRAIN AWARENESS WEEK NIDA scientist Dr. Allison Hoffman (right) explains the rules of the Brain Derby to a group of fifth-grade students as Dr. Cathrine Sasek of the Office of Science Policy and Communications looks on.

Groups of students rotated through nine activities there, each lasting about 20 minutes. For instance, they watched a "tumor" being surgically removed from a Jell-O brain, built a model brain, and learned the functions of each lobe when healthy and when injured or diseased.

In one of the NIDA-sponsored activities—called "Are You Smarter Than a Neuroscientist?"—two teams of students competed to answer computer-generated questions about the brain and the effects of drugs on the brain.

To start, a NIDA official clicked a mouse and a multiple-choice question appeared on the screen. Each team took turns answering. Some of the questions seemed easy—e.g., Addiction occurs when a person:

(a) can stop doing something (like take drugs) whenever they want;
(b) cannot stop doing something even though they may want to;
(c) uses illegal drugs;
(d) takes a drug once.

Others were clearly challenging—e.g., Marijuana can change learning and memory by acting in which part of the brain?

(a) Hippocampus
(b) Brain stem
(c) Visual cortex
(d) All of the above

If the team chose (b) in the first example or (a) in the second, "Congratulations, you got it right" would appear on the screen, and that team would earn a point.

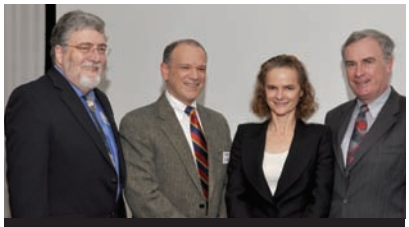
In a second game, "Welcome to Roger's Party," students took turns putting on a pair of goggles that simulated the disorienting effects of alcohol or drug intoxication. They then tried to navigate an obstacle course.

Dr. Roger Sorensen of NIDA's Division of Basic Neuroscience and Behavioral Research began each session by asking the students what they knew about the effects of alcohol and drugs. Their responses prompted a discussion about the dangers of substance abuse and gave him a chance to affirm or correct perceptions.

The students' experiences with the goggles reinforced the discussion. Dr. Sorensen explains: "After a student gets a turn wearing the goggles and walking around the maze, I ask him or her how it feels. The typical response is, 'I felt dizzy. I didn't like it.'"

Brain Awareness Week is an annual event, sponsored by the Dana Alliance for Brain Initiatives, to educate the public about brain science. The program is designed especially for middle school students, but this year's attendees ranged from the 5th through the 12th grade. About 20 public and private schools and six home-school networks in Maryland, Virginia, and the District of Columbia participated in the program.

New Advisory Council Members



NIDA ADVISORS (Left to right) Dr. R. Dale Walker, Dr. Eric J. Nestler, NIDA Director Dr. Nora D. Volkow, and Dr. James L. Sorensen.

NIDA announced the addition of three new members to its National Advisory Council on Drug Abuse at its February meeting:

R. Dale Walker, M.D., is a professor of psychiatry and of public health and preventive medicine at Oregon Health & Science University, as well as director of OHSU's Center for American Indian Health, Education and Research. He also directs the One Sky Center, a national resource for improving prevention and treatment of substance abuse and mental illness among American Indians and Alaska Natives.

Eric J. Nestler, M.D., Ph.D., is chairman of the Department of Neuroscience and director of the Brain Institute at the Mount Sinai School of Medicine in New York. Understanding the molecular mechanisms of addiction and depression is a major focus of his research, which uses animal models of these disorders to identify how stress and drugs of abuse change the brain and lead to addiction- or depression-like syndromes.

James L. Sorensen, Ph.D., is a professor of psychiatry at the University of California, San Francisco and the San Francisco General Hospital. He also directs the California-Arizona node of the NIDA Clinical Trials Network. Dr. Sorensen's research targets effective ways to integrate scientific findings into substance abuse treatment and to prevent and treat AIDS and other infectious diseases in drug-using populations.

YOUNG SCIENTISTS HONORED At this year's Intel International Science and Engineering Fair, NIDA's Dr. Lucinda Miner (far left) poses with Addiction Science Award winners (left to right) Lucia Mocz, Jada Nicole Dalley, Sehar Anjum Salman, and Daniel Jeffrey Martin.

NIDA Awards Prizes at International Science Fair

NIDA and Friends of NIDA, a nonprofit group that supports the Institute's mission, honored four high school students with Addiction Science Awards at this year's Intel International Science and Engineering Fair (ISEF), the world's largest science competition for high school students. At an awards ceremony on May 14, NIDA recognized the students for projects that showed innovation and creativity.

Addiction Science Awards are designed to encourage young investigators to consider addiction science as a field of study. This year, more than 1,500 students from more than 50 countries participated in the ISEF competition in Reno, Nevada.

The winners were:

First Place: Sehar Anjum Salman and Jada Nicole Dalley, both 16-year-old juniors at Keystone High School in San Antonio, Texas, earned the top award and will share a $2,500 scholarship. Their project was titled "A Cytogenic Analysis of Genetic Mutation Induced by Cigarette Smoke in *Drosophila Melanogaster*." The young collaborators observed a high rate of visible mutations in fruit flies that were exposed as larvae to a piece of foam saturated with tobacco smoke. The results suggest that fruit flies are affected negatively by third-hand smoke—the particles left behind by cigarette smoke on items like clothing, furniture, and draperies.

"What impressed us most about these young scientists was their ability to design and complete an extremely successful scientific project without having access to a college-level laboratory," says NIDA Director Dr. Nora D. Volkow.

Second Place: Daniel Jeffrey Martin, a 17-year-old junior from Desert Vista High School in Phoenix, Arizona, won the second-place award and $1,500 for "The Effect of Human Methamphetamine Usage on Carnivore Scavenging." The young scientist conducted a retrospective analysis of data from a local medical examiner's office to demonstrate that carnivorous animals do not like to scavenge the remains of humans known to have abused methamphetamine.

"Daniel Martin took something that had been forensic lore and turned it into a very interesting project that could have implications for forensic science," says Dr. Lucinda Miner, deputy director of the NIDA Office of Science Policy and Communications, who helped evaluate the student projects at the Intel competition.

Third Place: Lucia Mocz, an 18-year-old senior at Mililani High School in Mililani, Hawaii, earned the third-place award and $1,000 for "Complex Evaluation of Danger and Tranquility in Urban Settings: An Immunocomputing Intelligence Approach." Her project used an artificial intelligence algorithm to generate highly detailed maps with correlated indicators of danger and tranquility in the urban region of her home town.

"Although this brilliant young woman developed a tool with many universal applications, our judges recognized a provocative strategy that could one day help us better understand how the built environment relates to patterns of drug abuse," says Dr. Volkow. ■

United States Ranks First in Lifetime Use of Three Drugs

The proportion of people in the United States who have used cocaine at some time during their lives is higher—by a factor of four—than in 16 other nations surveyed by the World Health Organization (WHO). The United States also leads in lifetime use of cannabis and tobacco.

NIDA scientists suggest that the high U.S. rates are, in part, artifacts of drug epidemics of the 1970s and 1980s, and they note that U.S. drug use rates are now lower.

Between 2001 and 2006, WHO researchers asked 54,069 people about their lifetime exposure to cocaine, cannabis, tobacco, and alcohol. The survey is the first to publish directly comparable self-report data from a large number of countries. The analysis includes data from the first 17 countries participating in the WHO World Mental Health Survey Initiative.

Sixteen percent of U.S. respondents said they had ever used cocaine, as compared with about 4 percent of people surveyed in Colombia, Mexico, New Zealand, and Spain. Rates of lifetime cocaine use dipped much lower in the other nations. For cannabis, New Zealand is the only nation to nearly match the U.S. rate of 42.4 percent. Lifetime tobacco use in the United States is 73.6 percent, with Lebanon next, at 67.4 percent.

Rates of lifetime alcohol use, which exceed 90 percent in 8 of the 17 countries surveyed, are far higher than for the three other substances. Ukraine reports the highest rate (97 percent), and the United States ranks sixth with 91.6 percent. Alcohol use is much more common in the Americas, Europe, Japan, and New Zealand than in Africa, China, and the Middle East.

LIFETIME VERSUS CURRENT USE

The WHO survey did not query past-year or current substance use as do most U.S. nationwide surveys. "A survey of lifetime use does not provide the entire picture because it does not reflect current use or trends over time," notes NIDA Director Dr. Nora D. Volkow. "For example, although lifetime use of tobacco was reported by this study to be roughly 74 percent in the United States, current use has been documented at approximately 30 percent."

Dr. Wilson Compton of NIDA's Division of Epidemiology, Services and Prevention Research agrees that the study "does not take into account improvements in current drug use." But the fundamental finding that drug-use rates are generally higher in the United States than in most other countries has been confirmed, he says, by indirect indicators, such as drug-treatment admissions, hospitalization rates, and criminal justice data published by the United Nations Office on Drugs and Crime.

USE OF ADDICTIVE SUBSTANCES AROUND THE WORLD
Among 17 nations surveyed by the World Health Organization, the United States ranks first in lifetime use of three substances—cocaine, cannabis, and tobacco—and is in sixth place for alcohol use. The five highest rates of use in each drug category appear in red. Rates are reported as percentages.

Country	Cocaine	Cannabis	Tobacco	Alcohol
Colombia	**4.0**	10.8	48.1	**94.3**
Mexico	**4.0**	7.8	**60.2**	85.9
US	**16.2**	**42.4**	**73.6**	91.6
Belgium	1.5	10.4	49.0	91.1
France	1.5	**19.0**	48.3	91.3
Germany	1.9	**17.5**	51.9	**95.3**
Italy	1.0	6.6	48.0	73.5
Netherlands	1.9	**19.8**	**58.0**	**93.3**
Spain	**4.1**	15.9	53.1	86.4
Ukraine	0.1	6.4	**60.6**	**97.0**
Israel	0.9	11.5	47.9	58.3
Lebanon	0.7	4.6	**67.4**	53.3
Nigeria	0.1	2.7	16.8	57.4
South Africa	0.7	8.4	31.9	40.6
Japan	0.3	1.5	48.6	89.1
People's Republic of China	0.0	0.3	53.1	65.4
New Zealand	**4.3**	**41.9**	51.3	**94.8**

Dr. Compton suggests that one reason for the high U.S. lifetime rates might be that drug-use epidemics in the United States, including a major cocaine epidemic in the 1970s and another in the late 1980s, preceded those of other nations by a decade or more. "For people of middle age, lifetime exposure [to cocaine] in the United States would be greater than for the rest of the world," he says. "The differences are less pronounced when you look at young people."

OTHER FINDINGS

The WHO researchers report substance-use patterns that transcend national boundaries. Among them:

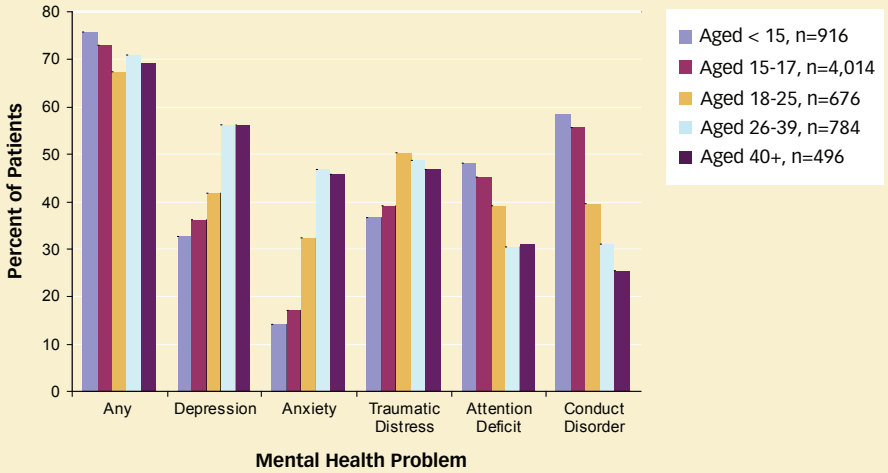
- The period of high risk for initiating use of the surveyed substances—previously late adolescence through the early 20s—now extends into the late 20s.
- Men are more likely than women to use cocaine, cannabis, tobacco, and alcohol, but this gender gap appears to be narrowing in the younger cohorts. Dr. Compton says one factor in gender-based patterns is opportunity to use. "In the past, adolescent boys had more exposure than girls," he says. "Given equal opportunity to use drugs, the rates are similar."
- The higher a person's income, the more likely he or she is to use each of the four substances surveyed. ■

SOURCE

Degenhardt, L. et al. Toward a global view of alcohol, tobacco, cannabis, and cocaine use: Findings from the WHO World Mental Health Surveys. *PLoS Medicine* 5(7):1-14, 2008.

WHAT THE NUMBERS SAY

Most People Entering Drug Treatment Have Additional Mental Health Problems



In 77 studies that included 4,930 adolescents and 1,956 adults, two-thirds of patients entering substance abuse treatment programs reported at least one co-occurring mental health problem during the previous year. Attention deficit and conduct disorders were most common in young patients, anxiety and depression in older patients.

Source: Chan, Y.F., Dennis, M.L., and Funk, R.L. Prevalence and comorbidity of major internalizing and externalizing problems among adolescents and adults presenting to substance abuse treatment. *Journal of Substance Abuse Treatment* 34(1):14-24, 2008.

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